PMC54

### TREATMENT SATISFACTION INSTRUMENTS FOR DIFFERENT PURPOSES DURING A PRODUCT'S LIFECYCLE—KEEPING THE END IN MIND

Rofail D[1], Regnault A[2], Taylor F[1], Filonenko A[3]
[1]Mapi Values Ltd, Bollington, Cheshire, UK; [2]Mapi Values, Lyon, France; [3]Bayer Schering Pharma AG, Berlin, Germany

**OBJECTIVES:** There are three main parts during a product's lifecycle when satisfaction instruments are particularly useful. These are to aid: 1) getting the product to the market; 2) getting the market to the product; and 3) demonstrating value for health care practitioners during daily clinical practice. This study investigates whether the development and implementation of treatment satisfaction instruments during a product's lifecycle are informed by their purpose. **METHODS:** A literature review was performed between 2000 and 2010 using electronic databases (PUBMED, PsycINFO, and EMBASE) and keywords such as "satisfaction" and "medication" or "drug" and "questionnaire." Relevant articles were reviewed in detail to extract information regarding the satisfaction instrument used, its development and validation, and when the instrument was used during a product's lifecycle. Additional information was collated including the type of studies the instruments were used in, clinical condition/indication, type of data generated (e.g. descriptive), and whether satisfaction was associated with other endpoints. **RESULTS:** Of 875 abstracts, 105 articles were further considered. The review indicated similarities regarding the development and validation of satisfaction instruments, such as using patient input to derive the items and exploring classical measurement properties specific to the target population. However, the specificities of the implementation of treatment satisfaction during the three main stages of a product's lifecycle were rarely considered. **CONCLUSIONS:** The development and implementation of treatment satisfaction instruments during a product's lifecycle rarely consider the purpose. By "keeping the end in mind," data from treatment satisfaction instruments can help three key parts: 1) getting the product to the market thus helping to generate evidence as part of an overall value proposition; 2) getting the market to the product; and 3) demonstrating the value to clinical practice. Furthermore, the development, validation and interpretation of scores from treatment satisfaction instruments should be sensitive to the intended purpose.

## CONCEPTUAL PAPERS & RESEARCH ON METHODS – Statistical Methods

PMC55

### SYSTEMATIC REVIEW OF METHODS FOR META-ANALYSIS AND INDIRECT COMPARISON USED IN EXISTING SYSTEMATIC REVIEWS AND HTA REPORTS—RESULTS FROM THE FIRST PART OF EBAYESMET PROJECT

Walczak J[1], Borowiack E[1], Kowalska M[1], Nikodem M[2], Zapalska A[1]
[1]Arcana Institute, Cracow, Poland; [2]CASPolska, Myslenice, Poland

**OBJECTIVES:** To collect information serve as a background for further activities of the eBayesMet project. To perform assessment of the frequency of use the particular statistical methods for meta-analyses and indirect comparisons in existing systematic reviews and HTA reports. **METHODS:** Database of Reviews of Effectiveness (DARE) was searched for relevant reviews published between January 2009 and March 2010. **RESULTS:** The majority of meta-analyses were prepared by using direct statistical methods (97%). The most popular expression about fixed model was that fixed effect model with the Mantel-Haenszel was used (36%). In case of random model, information that method DerSimonian Laird was selected (38%) was used most often. Meta-analyses were prepared mostly based on randomized controlled trials (87%) and in 3% only on observational studies. In meta-analyses based on RCTs in 42% of cases authors mentioned that to make strong conclusion more studies were needed. Employing Bayesian methods was generally very rare. For indirect comparisons six methods were recognized and the most common type was MTC Bayesian Model (53%). Observational studies were not included in any identified analysis. In 40% of the review information indicating the need for additional studies was contained. **CONCLUSIONS:** Our systematic reviews demonstrates a wide range of approaches and methods for conducting meta-analyses and indirect comparison used in current practice. The most popular approach for indirect comparison is Bayesian included network and MTC (over 65%). However performed analysis indicated that Bayesian approach is still marginal methods for performing direct comparison based on head to head studies. Bayesian models have essential advantage: some additional data can be included (as a prior distribution). This extra information can be for instance data from observational studies. However it should be emphasized, that in the analyzed random sample of systematic reviews studies other than RCT were included in only 13%.

PMC56

### IMPROVED SURVIVAL CURVE FITS TO SUMMARY DATA FOR ECONOMIC EVALUATIONS

Hoyle MW
University of Exeter, Exeter, UK

**OBJECTIVES:** Estimates of mean cost and quality-adjusted-life-years are central to the cost-effectiveness analysis of health technologies. They are often calculated from curve fits to overall survival and time on treatment, ideally by the method of maximum likelihood applied to individual patient data. However, such data is often not available. Instead, curves are commonly fit to summary Kaplan-Meier estimators, either by regression of the transformed estimator or by minimizing the sums of squares of differences between actual and fitted values. However, the tail of the estimator is often uncertain due to small numbers of patients at risk, and the curve fits do not yield estimates of the true uncertainty in survival times, which is a very important component of overall uncertainty in cost-effectiveness. Here, I describe a new, more accurate method of fitting survival curves to summary survival data. **METHODS:** First, I estimate the underlying individual patient data from the Kaplan-Meier estimator, numbers of patients at risk and from other published trial-related information. The fitted curve is then estimated by maximum likelihood given the estimated underlying individual patient data. **RESULTS:** Simulation applied to individual patient data shows that the method tends to give a more accurate curve fit than the traditional methods of fitting to the Kaplan-Meier estimator. Furthermore, the curve fit is often very similar to that derived by fitting to the underlying individual patient data by maximum likelihood. The method naturally yields accurate estimates of the uncertainty in survival times. When applied to economic evaluations submitted to NICE, the method often yields substantially improved estimates of cost-effectiveness compared to estimates based on fitting survival curves in the traditional manner. This highlights the sensitivity of many cost-effectiveness analyses to curve fits. **CONCLUSIONS:** When only summary survival data is available, I recommend the method for cost-effectiveness analysis.

PMC57

### BIAS IS WORSE THAN NOISE: HANDLING MISSING DATA FOR CONFOUNDERS IN OBSERVATIONAL STUDIES

Elkin EP, Exuzides AK, Pasta DJ, Miller DP
ICON Clinical Research, San Francisco, CA, USA

**OBJECTIVES:** Outcomes research often employs observational designs (e.g., disease registries, administrative health care data sets, chart reviews). Researchers using observational data may find various amounts of missing data for confounders when analyzing the association between an exposure (such as treatment use) and an outcome (such as an adverse event). This abstract examines the case when a potentially important confounding variable has a large amount of missing data and compares the analytic methods that may be used in this situation. **METHODS:** Strategies for handling missing confounder information include: (1) ignore confounders with lots of missing values; (2) exclude cases that are missing a confounder value; (3) impute a value for the confounder; (4) include missing as a separate category in the analysis. Data from a disease registry were used as the basis for simulations to compare the odds ratio for risk of death in patients who received a treatment compared to those without treatment. Both a clinical measurement and a subjective physician assessment are known to confound the relationship between treatment and death. **RESULTS:** The most problematic pattern of missing data was informative missing data. In one simulation, the clinical measurement was a strong predictor of death; however, it was disproportionately missing in patients who had died. The physician assessment predicted death strongly among patients missing the clinical measurement, but only weakly in patients not missing the clinical data. Different approaches to the missing confounder data either exacerbated or ameliorated the problem. **CONCLUSIONS:** Excluding cases can create misleading results due to selection bias. Combining all missing values into a separate category can create data "noise" (i.e., classification error); however, this may be the most transparent strategy and least likely to bias results. It is important to include all cases and all potential confounders in the analysis of outcomes research studies.

PMC58

### SYSTEMATIC REVIEW OF STATISTICAL METHODS OF META-ANALYSIS AND INDIRECT COMPARISON POTENTIALLY AVAILABLE TO USE IN SYSTEMATIC REVIEWS—RESULTS FROM THE FIRST PART OF EBAYESMET PROJECT

Walczak J[1], Nikodem M[2], Siedmiogrodzki K[2], Zapalska A[1], Borowiack E[1]
[1]Arcana Institute, Cracow, Poland; [2]CASPolska, Myslenice, Poland

**OBJECTIVES:** To collect information serve as a background for further activities of the eBayesMet project. To identify statistical methods and approaches for performing meta-analyses and indirect comparisons. To describe limitations and mathematical background, to discuss advantages and disadvantages of identified methods. **METHODS:** Databases such as MathSciNet, Medline and Cochrane Methodology Group resources, textbooks, guidelines for preparing systematic reviews were searched. We focused on papers with strictly mathematical descriptions of presented methods. **RESULTS:** Eleven main statistical methods were identified. There were six methods of meta-analysis (Inverse Variance, Mantel-Haenszel, DerSimonian-Laird, Peto, Bayesian and Generalized Linear Mixed Models for direct comparison), and five methods of indirect and mixed comparison (Bûcher, Minimal Squares, Lumley, Bayesian Mixed Treatment Comparison and Generalized Linear Mixed Models for indirect comparison). Moreover, there are different variants of some of these methods. For any type of analysis (direct, indirect, network, fixed, random, etc.) and any given data, there is an adequate version of Bayesian method for performing estimation. We found the Bayesian approach to be generally the most flexible.Analysis of precision and credibility of all identified statistical methods of meta-analysis and indirect comparison will be prepared in the next part of eBayesMet project. **CONCLUSIONS:** There are several statistical methods for performing proper data analysis in any model. The problem is with choosing optimal one for the given data set. On the other hand, all methods are less reliable and accurate for samples of data, especially for small (or zero) number of events in one or both arms. There is variety of statistical methods combining direct and indirect evidence, from which the most flexible is Mixed

Treatment Comparison using the Bayesian approach. Nevertheless, for each of these methods there are specific assumptions which have to be satisfied in order to obtain correct estimation.

## CONCEPTUAL PAPERS & RESEARCH ON METHODS – Study Design

**PMC60**

### INCLUSION OF CONFERENCE ABSTRACT DATA IN SYSTEMATIC REVIEWS OF PHARMACOLOGIC INTERVENTIONS IN DIFFERENT DISEASE AREAS

Zhang Y
Heron Evidence Development Ltd, Luton, England, UK

**OBJECTIVES:** Conference searching is a common part of systematic review methodology, this study investigates what proportion of study/trial data included in systematic reviews of pharmacologic interventions is derived solely from data published in conference abstracts, for 3 different disease areas. **METHODS:** The Cochrane Library of systematic reviews (SRs) was searched for SRs on pharmacologic interventions which state that they include conference abstracts in their Specialized Registers and include conference searching as part of the stated SR methods. Included studies lists of completed systematic reviews were reviewed and the total number of included studies and the number of studies for which data was obtained only from conference abstracts were extracted. In disease areas where a large number of SRs met the inclusion criteria, the 10 most recently published SRs were selected. The following disease groups were considered: psychological disease (depression and bipolar disorder), female cancers (breast cancer and ovarian cancer), and arthritis (osteoarthritis and rheumatoid arthritis). **RESULTS:** 3/10, 9/10 and 4/10 SRs contained studies solely from conference abstracts, for psychological disease, female cancers and arthritis respectively. For psychological disease 5% (5/226) of all studies included in 10 SRs came only from conference abstracts, for female cancers this was 14% (31/220) and for arthritis this was 14% (33/232). **CONCLUSIONS:** The proportion of studies from conference abstracts only included in SRs varies in the 3 examined disease areas. From these results, there is some evidence to suggest that the disease area of the review should inform the decision of whether to include conference searching as part of the protocol. To answer this question more conclusively, a more expansive review of SRs should be conducted covering a greater number of SRs and disease areas.

**PMC61**

### MONITORING OF HEALTH ECONOMIC DATA IN CLINICAL TRIALS

Bharmal M, Viswanathan S, Gemmen E
Quintiles, Rockville, MD, USA

**OBJECTIVES:** Health care decision makers are increasingly requesting health economic (HE) data, both to support product approval and for marketing purposes. Currently, there is limited information available to aid decisions surrounding the clinical monitoring of HE endpoints when they are collected as part of a clinical trial. It is necessary to understand the current level of monitoring activities surrounding HE data and evolve best practices for monitoring such data. **METHODS:** To better understand monitoring activities, a literature review was performed and qualitative in-depth interviews were conducted with six clinical research associates (CRA) who had experience collecting HE data as part of clinical trials in a range of therapy areas. The literature review and interviews focused on understanding current clinical trial monitoring practices, monitoring activities specific to HE data, the challenges faced during monitoring and recommendations for the future. **RESULTS:** All CRAs interviewed reported working either with patient-reported outcome (PRO) measures—quality of life questionnaires, patient diaries—and/or health care resource utilization data, in different therapy areas. Data monitoring activities in clinical trials can include a number of specific tasks ranging from full source data verification (SDV) to partial SDV to just checking for accuracy, legibility and completeness. The most common challenges in monitoring of HE data included incomplete questionnaires, misinterpretation of questionnaire data by the sites, and difficulty in SDV of health care resource utilization data by the CRA. Recommendations for the future included optimizing methods for documentation of health care resource utilization data, improving patient/site training in PRO use, and selecting the type of PRO and mode of PRO administration based on the patient population being examined. **CONCLUSIONS:** Health economic endpoints are increasingly being used in clinical trials, and CRAs are becoming familiar with PRO and health care resource utilization data. Monitoring activities for HE data vary by the study design and type of data collected.

## CARDIOVASCULAR DISORDERS – Clinical Outcomes Studies

**PCV1**

### ESTIMATION OF STROKE-RELATED ADVERSE EVENTS, HEALTH CARE UTILITY AND COST OF PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Wang L[1], Baser O[2]
[1]STATinMED Research, Ann Arbor, MI, USA; [2]STATinMED Research/University of Michigan, Ann Arbor, MI, USA

**OBJECTIVES:** To estimate mortality, health care utility and health care cost burden of patients who suffered a stroke during the 180 days after diagnosis of non-valvular atrial fibrillation (NVAF) and compare it with patients who did not suffer a stroke. **METHODS:** Based on 2005–2007 U.S. Medicare advantage insurance claim files, patients aged 65 years and older who had 2 or more primary diagnoses for NVAF within 30 days of one another were selected. The 180-day follow-up event rates, health care facility use and health care cost for patients with a stroke and those without were compared. Risk adjustment was done by using the propensity score matching method with the ProbChoice™ algorithm. **RESULTS:** Out of patients identified with NVAF (n = 18,575), 575 suffered a stroke during the 180 days after NVAF diagnosis. 94% (n = 541) did not have stroke during the baseline period (180 days before NVAF diagnosis). Patients were not significantly different in terms of gender, region, and baseline comorbid conditions. After risk-adjustment for pre-specified covariates, mortality (7.14% vs. 2.09% $P < 0.0001$), outpatient emergency room (ER) visits (79.97% vs. 46.34% $P < 0.0001$), acute coronary syndrome (43 vs. 16/100 person years), transient ischemic attack (73 vs. 4 /100 person years), major bleeding (85 vs. 4 /100 person years) and myocardial infarction (32 vs. 9/100 person years) were all higher for patients who suffered a stroke compared to those who did not. Besides inpatient cost ($24,116 vs. $20,828), risk-adjusted outpatient ER costs ($921 vs. $873) were also higher for stroke patients. Overall risk-adjusted difference in health care costs is significant ($33,430 vs. $16,375 $P < 0.0001$). **CONCLUSIONS:** Most of the adverse events analyzed were higher for patients who suffered a stroke after NVAF relative to patients who did not. Total health care utility and health care cost were also significantly increased.

**PCV2**

### ESTIMATION OF ADVERSE EVENTS IN 3 MONTHS AFTER VENOUS THROMBOEMBOLISM EVENT FOR MEDICARE PATIENTS WHO UNDERWENT HIP FRACTURE SURGERY

Wang L[1], Dysinger A[1], Baser O[2]
[1]STATinMED Research, Ann Arbor, MI, USA; [2]STATinMED Research/University of Michigan, Ann Arbor, MI, USA

**OBJECTIVES:** To estimate mortality, re-hospitalization and bleeding 180 days after a venous thromboembolism (VTE) event in patients following hip fracture surgery and to compare the outcomes with patients without VTE. **METHODS:** Based on 2004–2006 national Medicare claims, all patients who underwent hip fracture surgery were identified. a total of 180 days follow-up event rates for patients who had a VTE event during their initial hospitalization were calculated. Events were compared between patients who suffered a VTE event and those that did not. Risk adjustment was done using propensity score matching (using the ProbChoice™ algorithm) controlling for baseline demographic and clinical characteristics between patients with and without VTE. **RESULTS:** In patients who underwent hip fracture surgery (n = 77,743), 2.23% had post-operative VTE events during their initial hospitalization. Almost 72.96% (n = 1263) of these patients suffered deep vein thrombosis (DVT), 20.97% (n = 363) had a pulmonary embolism (PE), and 6.07% (n = 105) had both DVT and PE. After multivariate adjustment for pre-specified covariates, mortality was almost 50% higher for patients with VTE compared to those without VTE. Differences in mortality rate were more pronounced for PE patients, whom the event was associated with almost two-fold. The VTE group was more likely to be re-hospitalized in one year (odds ratio: 1.18, p = 0.2720). Bleeding was 1.8 times higher (p = 0.0080). **CONCLUSIONS:** VTE events during initial hospitalization for hip fracture surgery increased patients' mortality, re-hospitalization and bleeding compared to patients with no VTE events.

**PCV3**

### COMPARISON OF MORTALITY, HEALTH CARE UTILITY AND COST OF PATIENTS WITH WARFARIN TREATMENT FOR NON-VALVULAR ATRIAL FIBRILLATION VERSUS PATIENTS WITH OTHER TREATMENT

Wang L[1], Baser O[2]
[1]STATinMED Research, Ann Arbor, MI, USA; [2]STATinMED Research/University of Michigan, Ann Arbor, MI, USA

**OBJECTIVES:** To estimate the economic and clinical burden of patients who used warfarin during the 180 days after diagnosis of non-valvular atrial fibrillation (NVAF) and compare it with patients who did not use warfarin. **METHODS:** Based on 2005–2007 U.S. Medicare advantage insurance claim files, patients aged 65 years and older who have had 2 or more primary diagnoses for NVAF occurring within 30 days of one another were selected. The 180 days follow-up event rates, health care facility use and cost were compared. Risk adjustment was done by using the propensity score matching method with the ProbChoice™ algorithm. **RESULTS:** In patients who identified with NVAF (n = 18,575) 12,186 used warfarin during the 180 days after NVAF diagnosis and 6,389 used other drugs or did not use any drugs. Patients were significantly different in terms of age, gender, comorbid conditions and baseline CHADS score. After risk-adjustment for pre-specified covariates, mortality (0.75% vs. 2.26%), outpatient emergency room (ER) visits (48.79% vs. 53.30%), acute coronary syndrome (105 vs. 154 /100 person years), and myocardial infarction (61 vs. 112 /100 person years) were all lower for patients who had warfarin with non-valvular atrial fibrillation. Even though drug cost is higher for the warfarin group ($1,687 vs. $1,595), risk-adjusted outpatient ER costs ($756 vs. $861) were lower. Overall risk-adjusted health care costs did not differ ($12,739 vs. $15,359). **CONCLUSIONS:** Most of the adverse events analyzed were lower for patients who had warfarin after non-valvular atrial fibrillation relative to patients who did not. However, the economic burden of both groups of patients on the health care system was similar.